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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,791	11/12/2003	Christopher William Aston	WYE-076	8289

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	
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08/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,791	ASTON ET AL.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE filed on May 21, 2007 and the amendment filed on February 26, 2007 have been entered. The claims pending in this application are claims 32-36. Rejection and /or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on February 26, 2007.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Written Description

Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the interim guidelines on written description published on December 21, 1999 in the Federal Register at Volume 64, Number 244, pp.71427-71440.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed". *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification (for example, see page 60) provides adequate written descriptions for NBI-31772, which is a nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP). However, the specification fails to adequately describe any kind of nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) as recited in claims 32-36. The claimed inventions as a whole are not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed inventions as a whole) such that a person skilled in the art would recognize that the inventor had

possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998).

In this instant case, since the specification does not have a definition for "nonpeptide small molecule", the nonpeptide small molecule recited in claims 32-36 is read as any kind of nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) wherein the nonpeptide small molecule can be a chemical compound, metal complex, lipid, nucleic acid and its analogs. Although the specification (for example, see page 60) provides adequate written descriptions for NBI-31772, which is a nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), the specification does not provide adequate written descriptions any kind of nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP). For example, the specification does not describe the lead molecules 1 and 2 taught by Chen *et al.*, (Journal of Medicinal Chemistry, 44(23):4001-4010, 2001) wherein the lead molecules 1 and 2 are nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP). Although page 66, lines 28-30 of the specification describes that the paper from Chen *et al.*, (Journal of Medicinal Chemistry, 44(23):4001-4010, 2001), page 66, lines 28-30 of the specification is the title of the reference recited in the specification and is not part of the invention of this instant application. Furthermore, nowhere in the specification describes that the paper from Chen *et al.*, is incorporated by reference. Therefore, claims 32-36 encompass numerous unknown and

unidentified nonpeptide small molecules which dissociate a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) that miss from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

With limited disclosure provided by the specification, the skilled artisan cannot envision all nonpeptide small molecules recited in claims 32-36 and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. Enablement

This rejection is based on that a pharmaceutical composition recited in claims 32-36 is read as a composition used for the purpose of treating a disease.

Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that a composition recited in claims 32-36 can be used as a pharmaceutical composition. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a composition recited in claims 32-36 can be used as a pharmaceutical composition.

Claims 32-36 are directed to a pharmaceutical composition comprising any kind of pharmaceutically acceptable carrier and any kind of nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) wherein the composition is formulated to be compatible with an intended route of administration to any kind of subject. A pharmaceutical composition is read as a composition used for the purpose of treating a disease. Although the specification describes that dose-dependent inhibition of ^{125}I IGF-I binding to IGFBP-1 to IGFBP-6 by NBI-31772 (see Figure 8 and Example 8 in page 60 of the specification), the nonpeptide small

molecule recited in claim 32 is not limited to NBI-31772 and can be read as some other nonpeptide small molecule which is not NBI-31772. Furthermore, the specification does not show that the compositions recited in claims 32-36 can be used for treating any kind of disease and a composition comprising NBI-31772 can be used for treating any kind of disease. In view of claims 32-36, it is unclear how the compositions recited in claims 32-36 can served as a pharmaceutical composition.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art. The undue experimentation at least includes to test whether the composition recited in claims 32-36 can be used for treating any kind of disease so that such composition can served as a pharmaceutical composition.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu *et al.*, (The Journal of Biological Chemistry, 35, 32419-32422, August 2001).

Regarding claims 32 and 33, since Liu *et al.,* teach that ki for binding of NBI31772 to IGFBP-2 is 1.18±0.27 nM and NBI31772 inhibits the binding of ^{125}I IGF-I binding to IGFBP-2 (see Figure 2 and Table II in page 32421), Liu *et al.,* disclose a pharmaceutical composition comprising a pharmaceutically acceptable carrier (ie., serum-free DMEM) and a nonpeptide small molecule (ie., NBI-31772) which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), wherein the composition is formulated to be compatible with an intended route of administration to a subject (ie., pipetting to the cultured fibroblast cells) as recited in claim 32 wherein the protein complex is further defined as a dimeric complex comprising IGF and IGFBP as recited in claim 33 (see Figure 2 and Table II in page 32421 and left column in page 32420).

Regarding claim 34, since claim 32 is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), wherein the composition is formulated to be compatible with an intended route of administration to a subject and the protein complex recited in claim 32 is not a part of structural limitations of claim 32, and NBI-31772 taught by Liu *et al.,* has an ability to dissociates a protein complex comprising an IGF and an IGFBP or IGFBP-2 and ALS, Liu *et al.,* disclose that the protein complex further comprises an acid labile subunit (ALS), wherein the ration of IGF to IGFBP to ALS is 1:1:1 as recited in claim 34.

Regarding claim 35, since Liu *et al.,* teach to dilute NBI-31772 in serum-free DMEM before adding to the cultured fibroblast cells (see left column in page 32420) and cell culture

must be performed in a sterile environment, the composition comprising serum-free DMEM and NBI-31772 taught by Liu *et al.,* must be sterile as recited in claim 35.

Regarding 36, since the composition taught by Liu *et al.,* comprises serum-free DMEM and NBI-31772 (see left column in page 32420), DMEM is Dulbecco's modified Eagle's medium (see page 32419, left column) and the word "edible" in web is defined as "suitable for use as food" (see attached definition for "edible"), Liu *et al.,* teach that the composition is formulated to be compatible with oral administration (ie., oral administration to an animal) and the pharmaceutically acceptable carrier is edible (ie., serum-free DMEM serving as a food for feeding the cultured fibroblast cells) as recited in claim 36.

Therefore, Liu *et al.,* teach all limitations recited in claims 32-36.

Response to Arguments

In page 4, second paragraph bridging to page 5, first paragraph of applicant's remarks, applicant argues that "[L]iu does not teach the claimed *pharmaceutical compositions.* Liu teaches NBI-31772 and its use in *in vitro* studies, one involving a mixture with a radioactive IGF-1 protein and one involving administration to mouse fibroblast cells being cultured in flasks in the presence of fetal bovine serum, culture medium, IGFBP-3 isolated from outdated human plasma, and IGF-l. Liu does not administer a composition to a subject. Liu provides no indication that any of its NBI-31772 compositions have been formulated to be compatible with administration to a subject (making no reference, for example, to sterility, purity of ingredients, *etc.).* Liu does not indicate that any of its NBI-31772 compositions would be pharmaceutically effective".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since the composition comprising serum-free DMEM and NBI-31772 taught by Liu *et al.,* (see left column in page 32420) can be pipetted to the cultured fibroblast cells or is used for oral feeding an animal, Liu *et al.,* do teach that the composition is formulated to be compatible with an intended route of administration to a subject (ie., the cultured fibroblast cells or an animal) as recited in claim 32. Second, the claims do not require that the composition is pharmaceutically effective as argued by applicant.

7. Claim 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen *et al.,* (J. Med. Chem., 44, 4001-4010, October 3, 2001).

Regarding claims 32 and 33, since Chen *et al.,* teach compounds 1 and 2 inhibit the binding of ^{125}I IGF-I binding to IGFBP-1 to IGFBP-6 (see abstract in page 4001, scheme 1 in page 4002, Figure 1 page 4005 and Table 4 in page 4007), Chen *et al.,* disclose a pharmaceutical composition comprising a pharmaceutically acceptable carrier (ie., serum-free DMEM) and a nonpeptide small molecule (ie., compound 1 or 2) which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), wherein the composition is formulated to be compatible with an intended route of administration to a subject (ie., pipetting to the cultured fibroblast cells) as recited in claim 32 wherein the protein complex is further defined as a dimeric complex comprising IGF and IGFBP as recited in claim 33 (see abstract in page 4001, scheme 1 in page 4002, Figure 1 page 4005, Table 4 in page 4007 and right column in page 4009).

Regarding claim 34, since claim 32 is directed to a pharmaceutical composition

comprising a pharmaceutically acceptable carrier and a nonpeptide small molecule which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP), wherein the composition is formulated to be compatible with an intended route of administration to a subject and the protein complex recited in claim 32 is not a part of structural limitations of claim 32, and compound 1 or 2 taught by Chen *et al.,* has an ability to dissociates a protein complex comprising an IGF and an IGFBP (ie., IGFBP-2) and ALS, Chen *et al.,* disclose that the protein complex further comprises an acid labile subunit (ALS), wherein the ration of IGF to IGFBP to ALS is 1:1:1 as recited in claim 34.

Regarding claim 35, since Chen *et al.,* teach to dilute compound 1 or 2 in serum-free DMEM before adding to the cultured fibroblast cells (see right column in page 4009) and cell culture must be performed in a sterile environment, the composition comprising serum-free DMEM and compound 1 or 2 taught by Chen *et al.,* must be sterile as recited in claim 35.

Regarding 36, since the composition taught by Chen *et al.,* comprises serum-free DMEM and compound 1 or 2, DMEM is a cell culture medium (see right column in page 4009) and the word "edible" in web is defined as "suitable for use as food" (see attached definition for "edible"), Chen *et al.,* teach that the composition is formulated to be compatible with oral administration (ie., oral administration to an animal) and the pharmaceutically acceptable carrier is edible (ie., serum-free DMEM serving as a food for feeding the cultured fibroblast cells) as recited in claim 36.

Therefore, Chen *et al.,* teach all limitations recited in claims 32-36.

Conclusion

8. No claim is allowed.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

July 30, 2007

FRANK LU
PRIMARY EXAMINER